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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: David BERD

Serial No.: 08/203,004 Art Unit: 1642

Confirmation No.:

Filed: February 28, 1994 Examiner: Susan UNGAR

For: COMPOSITION AND METHOD OF USING TUMOR CELLS

BRIEF ON APPEAL

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

December 28, 2001

Sir:

This Brief on Appeal (submitted in triplicate) follows the Notice of Appeal filed May 29, 2001 and the response to the Final Office Action mailed on November 29, 2000. Appellant submits concurrently herewith (1) a Petition for Extension of Time for a period of five months (from July 29, 2001 up to and including December

31, 2001, as December 29 falls on a Saturday) accompanied by the required fee; and (2) the required fee for this Brief. It is believed that no additional fees are required for these submissions. However, should it be determined that additional fees are required or that any refund is due in connection with this application, the Commissioner is hereby authorized to charge the required fee(s) and/or credit the refund(s) due to Deposit Account No. 04-0100.

1. The Real Party in Interest

Thomas Jefferson University (TJU), Philadelphia, Pennsylvania, is the assignee of this application. Avax Technologies, Inc., of Overland Park, Kansas (Avax), has an exclusive license from TJU. Accordingly, Avax is a real party in interest.

2. Related Appeals and Interferences

There are no related appeals or intereferences.

3. Status of Claims

Claims 43, 44, 47, 49-62, 64-72, and 74-77 are pending and the final rejection of all of these claims is the subject of this Brief. A copy of the pending claims is attached as an Appendix immediately following this Brief.

4. Status of Amendments

Appellant filed an amendment May 29, 2001 in response to the Final Office Action dated November 29, 2000. The Examiner entered this amendment pursuant to the Advisory Action dated July 5, 2001 (copy attached as Exhibit 1).

5. Summary of the Invention

The present invention concerns a composition comprising human tumor cells (other than melanoma cells) conjugated with a hapten.[1] Such haptenized tumor cells have been surprisingly and unexpectedly discovered to form an effective immunogenic component in a vaccine composition for immunotherapy of cancer of the type from which the cells were derived. The haptenized tumor cells are obtained from the patient receiving treatment (i.e., they are "autologous"), and are rendered incapable of growing in the body of a human upon injection therein.

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[1] A hapten is a small molecule that, when conjugated to a carrier, can elicit a specific immune response. Preferred haptens include the highly reactive dinitrophenyl and trinitrophenyl groups. (Specification, page 15, lines 4-9).

In another aspect, the invention provides a method for treating a malignant tumor (other than melanoma) in a human patient by co-administering a composition comprising haptenized autologous human tumor cells of the same tumor type as the tumor in the patient, along with an adjuvant. The composition elicits at least one of the following upon administration to the patient with the adjuvant: an inflammatory immune response against the tumor of the patient; a delayed-type hypersensitivity response against the tumor of the patient; and activated T lymphocytes that infiltrate the tumor of the patient.

In a further aspect, the invention provides a method for treating a malignant tumor in a human patient by co-administering a composition comprising haptenized autologous human tumor cells of the same tumor type as the tumor in the patient, along with an adjuvant, at least six times. In still a further embodiment, the patient receives a dose of cyclophosphamide prior to the first administration of the composition.

The composition of the invention represents an advance over prior experiments involving haptenization of tumor and other cells for testing in animal models. Prior art experiments suggested that haptenization results in hapten-specific immunity. Such immunity would not proved useful for generating an effective immune response against metastasized tumor cells or tumor cells remaining after tumor resection because the residual tumor cells in a patient do not bear hapten.

The invention addresses a need in the art for an effective immunotherapy for tumors, especially non-melanoma tumors. Administering haptenized tumor cells unexpectedly increases the effectiveness of the resulting tumor-specific immune response, especially with six or more immunizations, resulting in a more effective immunotherapy. Most importantly, the inventor has discovered that the protective immunity is not hapten-specific, which the prior art suggested would be the case.

6. Issues

The only remaining issues in this application concern obviousness of the claims over various combinations of references as set forth below.[2]

a. The rejection over Murphy, Berd 1989, Geczy, and the Antibody Patents: Claims 47, 65-72 and74-77 stand rejected as allegedly being obvious (see

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[2] The Examiner withdrew the rejection of claims 43, 49-51, and 54-55 for allegedly not being enabled by the disclosure in the Advisory Action (Exhibit 1) in view of the amendment of claim 43 to recite that the composition of the invention elicits, when administered together with an adjuvant, an immune response. In a previous Office Action, the Examiner stated that the specification enables a method for treating a malignant tumor in a human patient comprising administering the composition of claim 43 (*i.e.*, haptenized autologous non-melanoma tumor cells) and BCG (Office Action dated April 28, 1999 [Exhibit __; Paper No. 36], paragraph No. 6). The specification supports this recitation, e.g., Examples 2 and 3 report eliciting a striking inflammatory response when the composition of the invention was administered together with the adjuvant BCG. Claims 49-51 and 54-55 depend from claim 43.

paragraph No. 5 of the Final Office Action [Exhibit 2], referencing Paper No. 41 [Exhibit 3], Section 5, pages 2-3 and Paper No. 36 [Exhibit 4], Section 10, pages 8-12) over Murphy et al. (Lab Invest 1990;62:70A; hereinafter "Murphy" [Exhibit 5]), in view of U.S. Patent No. 5,702,704 (hereinafter "'704 patent" [Exhibit 6]), U.S. Patent No. 5,626,843 (hereinafter "'843 patent" [Exhibit 7]), U.S. Patent No. 5,008,183 (hereinafter "'183 patent" [Exhibit 8]), or U.S. Patent No. 4,232,001 (hereinafter "'001 patent" [Exhibit 9]) (hereinafter collectively "the Antibody Patents"); Berd *et al.*, (Proc AACR 1989:30:382; hereinafter "Berd 1989" [Exhibit 10]), and Geczy et al. (J Immunol. 1970;19:189-203, hereinafter "Geczy" [Exhibit 11]).

b. The rejection over Berd 1989, the Antibody Patents, and Geczy: Claims 47, 65-72, and 74-77 stand rejected as allegedly being obvious over Berd 1989 in view of the Antibody Patents and Geczy (see paragraph 6 of the Final Office Action [Exhibit 2], referencing Paper No. 41 [Exhibit 3], Section 6, page 4 and Paper No. 36 [Exhibit 4], Section 11, pages 12-15).

c. The rejection over Berd 1989, the Antibody Patents, and Geczy in view of Wiseman: Claims 43, 44, 47, 49-62, 64-72, and 74-77 stand rejected as allegedly being unpatentable over Berd '89 in view of the Antibody Patents, and Geczy, in further view of Wiseman et al. (West J Med 1989;151:283-288, hereinafter "Wiseman" [Exhibit 12]) (see paragraph 7 of the Final Office Action [Exhibit 2],

referencing Paper No. 41 [Exhibit 3], Section 7, pages 4-5 and Paper No. 36 [Exhibit 4], Section 12, pages 15-18).

d. The rejection over Berd 1989, the Antibody Patents, Geczy, and Berd 1983: Claims 43, 44, 47, 49-62, 64-72, and 74-77 stand rejected as allegedly being unpatentable over Berd '89 in view of the Antibody Patents, and Geczy, in further view of Berd et al. (PASCO 1983;2:56, hereinafter "Berd 1983 [Exhibit 13]) (Final Office Action [Exhibit 2], paragraph No. 8, referencing Paper No. 41 [Exhibit 3], Section 8, page 6 and Paper No. 36 [Exhibit 4], Section 13, pages 18-21).

e. The rejection over Berd, the Antibody Patents, Geczy, and Sanda and Moody: Claims 43, 44, 47, 49-62, 64-72, and 74-77 remain rejected as allegedly being unpatentable over Berd '89 in view of the Antibody Patents, Geczy, in further view of Sanda et al. (J Cellular Biochem 1993;suppl.17D:120, hereinafter "Sanda" [Exhibit 14]) and Moody et al. (J Urol 1991;145:293A, hereinafter "Moody" [Exhibit 15]) (Final Office Action [Exhibit 2], paragraph No. 9, referencing Paper No. 41 [Exhibit 3], Section 9, page 7 and Paper No. 36 [Exhibit 4], Section 14, pages 21-25).

7. Grouping of Claims

The claims do not stand or fall together. Claims 43 and 49-55 are directed to compositions that have distinct features and patentability considerations. Within this group, claim 49 is directed to a Markush group of tumors that has distinct patentability considerations relative to the genus of tumors. In addition, claim 51 is directed to a specifically recited hapten.

Claims 44, 56-62, 64, and 76 are directed to a method for treating a malignant tumor in a human, which has distinct patentability considerations relative to the composition claims. Within this group, claims 56 and 57 are directed to a Markush group of tumors that has distinct patentability considerations relative to the genus of tumors. In addition, claim 59 is directed to a specifically recited hapten.

Claims 47, 65-72, 74, 75, and 77 are directed to a method for treating a malignant tumor in a human, which has distinct patentability considerations relative to the composition claims and to the other method of treatment claims because these claims (i) do not exclude treatment of melanoma tumors and (ii) require at least six administrations of the immunotherapy vaccine. The Examiner has rejected these claims for different reasons than the other claims, which further establishes that these claims stand or fall separately from the other claims. Within this group, claims 65 and 66 are directed to a Markush group of tumors that has distinct patentability considerations relative to the genus of tumors. In addition, claim 68 is directed to a specifically recited hapten. Finally, claim 70 recites a specific regiment for administration of cyclophosphamide (CY).

8. Argument

The relevant test for obviousness requires three basic factual inquiries: the scope and content of the prior art are to be determined; the differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the art resolved. *Graham v. Deere*, 383 U.S. 1, 17 (1966); *Ruiz v. A.B. Chance Co.*, 57 USPQ2d 1161, 1165 (Fed. Cir. 2000). The relevant inquiry involves three steps. First, there must be some suggestion or motivation to modify what is taught in a reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference or combination of references must teach all of the claim limitations. Both the motivation and the reasonable expectation of success must be found in the prior art, not in appellant's disclosure. *See*, MPEP § 2143, *citing In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As explained in detail below, the Final Office Action fails to establish a *prima facie* case for obviousness under these requirements. In particular, since Berd 1989 fails to provide any expectation of success, *i.e.*, clinical benefit, using the haptenized tumor cell approach in melanoma patients, this reference is completely irrelevant in providing any expectation of success for such an approach in other types of cancer. Since no other reference cited by the Examiner makes up for this

fundamental flaw, nor the combination of them (see below), obviousness does not obtain.

Given the prominence of Berd 1989 in each rejection, the Appellant would like to address the teachings of this reference, particularly through the lense of one of ordinary skill in the art, Dr. Donald Braun, who attended an interview with the Examiner and her supervisor on January 5, 2000.[3] To factually determine what a reference teaches one of ordinary skill in the art in implementing the Graham standard, the courts have relied upon affidavit evidence either by experts or those of ordinary skill in the art. *See In re Carroll* 202 USPQ 571 (CCPA 1979); *In re Piasecki*, 223 USPQ 785, 789 (Fed. Cir. 1984); *In re Oelrich*, 198 USPQ 210 (CCPA 1978). Furthermore, affidavits of those skilled in the art have been held to constitute factual evidence of the level of skill in the art. *E.g., In re Piasecki*, 223 USPQ at 789; *In re Oelrich*, 198 USPQ 210, 214-15. Such affidavits constitute competent evidence that cannot be ignored. *See e.g., Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 227 USPQ 657, 674-75 (Fed. Cir. 1985).

In all of the rejections, the Examiner relies on the Berd 1989 abstract as an allegedly successful example of treatment of melanoma by administration of DNP-conjugated autologous melanoma cells in connection with BCG and a preceding dose

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[3] Dr. Donald Braun has a long career in the field of immunological oncology, as evidence by his *curriculum vitae*, attached as Exhibit A to the Braun Declaration [Exhibit 16]. There can be no doubt as to his qualifications as one of at least ordinary skill in the art.

of cyclophosphamide. The Examiner also contends that it would have been expected that the autologous irradiated melanoma, lung, colon, kidney, and colon cancer cells of Wiseman ([Exhibit 11] discussed below) would be successfully substituted for the melanoma cells of Berd 1989 to treat other cancer types (Final Office Action [Exhibit 2], bridging paragraph between pp. 5 and 6). However, both of these conclusions depend on according more weight to the Abstract than one of ordinary skill at the time of the invention would have given it. As set forth by the Braun Declaration accompanying the response to the Final Office Action[4], Berd 1989 does not describe a successful immunotherapy for melanoma (Braun Declaration [Exhibit 16], paragraph 7). On the contrary, it represents a preliminary result that raises more questions and ambiguities than it answers. Early animal work on tumor immunotherapy could not establish whether similar approaches could work in humans (Braun Declaration [Exhibit 16], paragraph 8). The Abstract fails to provide a definitive protocol that would permit one to repeat the work, determine whether this approach elicited an immune response

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[4] The Braun Declaration memorializes comments made by Dr. Braun during THE personal interview with the Examiner and her Supervisor on January 5, 2001, at which this application and a number of related applications by the same inventor were discussed. The points made therein reinforce scientific and factual argument distinguishing the prior art of record already made by applications. The Examiner agreed at the interview that Dr. Braun's Declaration would substantiate these points. However, for reasons unknown to the Appellant, the Examiner stated in the Advisory Action (Exhibit 1) that she had not considered the Braun Declaration "... because Applicant has not shown good and sufficient reasons why it was not earlier presented..." (Advisory Action [Exhibit 1], page 2). It had seemed self-evident that presentation of this Declaration could not have preceded the clarification of issues achieved at the interveiw.

to unmodified cells, or establish that it achieved any clinical benefit (Braun Declaration [Exhibit 16], ¶¶ 9, 10, 11).

With these considerations in mind, we turn to the specific grounds for rejection.

a. The rejection of claims 47, 65-72 and 74-77 over Murphy, Berd 1989, Geczy, and the Antibody Patents

Claim 47 is directed to a method for treating a malignant tumor in a human patient by co-administering a composition comprising haptenized autologous human tumor cells of the same tumor type as the tumor in the patient, along with an adjuvant, at least six times. As disclosed in Examples 3, 4, and 6, administration of the immunotherapeutic vaccine comprising haptenized tumor cells on at least six, and in most cases eight, occasions resulted in actual treatment of tumors, with statistically significant greater cancer-free survival compared to controls (who received non-haptenized vaccine) at two years. (Specification, page 29, lines 22-25). The difference was highly significant. (*Id.*, page 30, lines 26-27; page 41, line 24 to page 42, line 8).

The Examiner states that Murphy teaches a method for treating melanoma comprising sensitizing with DNCB, administering a therapeutically effective amount of cyclophosphamide (CY), and administering a therapeutically effective amount of

autologous, irradiated DNP-conjugated melanoma cells mixed with BCG adjuvant. The Examiner notes that Murphy does not teach administration of at least six vaccine doses at spaced intervals, a specific dose of CY (300 mg/M^2), prior sensitization with 1-fluoro-2,4-dinitrobenzene, or eliciting certain specified immune responses against the tumor. The Examiner cites the Antibody Patents for teaching administration of at least six doses of antigen; Berd 1989 for teaching a successful method of treating melanoma with the specified dosage of CY using DNP-conjugated melanoma cells, and that Geczy teaches that halogenated dinitrobenzenes are commonly used to elicit delayed type hypersensitivity. (Paper 36 [Exhibit 4], pages 9-10). The thrust of this rejection, then, is that it would have been obvious from the combined teachings of Murphy, the Antibody Patents, and Berd 1989 to administer at least six doses of a haptentized tumor cell vaccine, and that various haptenization reagents can be used as describe by Geczy.

Appellant have previously argued that the references cannot be combined as suggested by the Examiner without employing impermissible hindsight from the disclosure of the invention. The Examiner contends that "[s]ome degree of hindsight is permissible in making rejections under 35 U.S.C. 103 since it must be recognized that any judgement on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning." (Final Office Action [Exhibit 2], page 3).

The teachings and deficiencies of Geczy have been discussed in Appellant's previous amendment, filed September 22, 2000, on pages 11-12, paragraphs 3.b.iii. Geczy indeed teaches the equivalency of DNCB and DNFB for the induction of DTH as stated by the Examiner, but proposes that direct haptenization of lymphocytes is necessary for lymphocyte transformation. Thus, to the extent that the teachings of Geczy relate to those of Berd 1989 and/or Murphy, they diverge and teach away from using haptens to elicit a protective immune response against unmodified tumor cells. Geczy relates to anti-hapten responses, which would hardly be relevant to anti-tumor responses elicited by haptenized tumor cells, but only for immune response towards the haptenized tumor cell vaccine itself.

With respect to the Antibody Patents, their teachings and deficiencies were also discussed in the previous amendment dated September 22, 2000, pages 10-11, paragraph 3.b.ii. The Examiner states that the '704 patent, '843 patent, '183 patent, and '001 patent teach conventional immunization schedules wherein antigen is administered at least six times at spaced intervals. Indeed, the '183 patent teaches an assay for detecting the presence or absence of antibodies that bind to a human retrovirus antigen. The '001 patent teaches non-human antibodies to estrophilin. The '843 patent teaches the use of antibodies as immunosorbents for the treatment of AIDS. The '704 patent teaches antibodies that recognize advanced glycosylation endproducts and methods of using the antibodies for the measurement of the amount of advanced glycosylation end products in plants, animals, and cultivated and

synthesized protein material. None of these patents contains an objective teaching of the use of antibodies for the treatment of human cancers. Even if these patents did teach antibody-based (passive) immunotherapy, Appellant submits that such teaching would have no bearing on the present invention, which concerns active specific immunotherapy to tumors.

Moreover, the Antibody Patents fail to suggest, and indeed teach away from, generating an immune response to a carrier, such as a tumor cell, by immunizing with a hapten. Such a result would actually be contrary to the teachings of these references. For example, advanced glycosylation endproducts are analogous to haptens: they are small molecules conjugated to carrier proteins. Following the teaching of the '704 patent, one would expect to generate antibodies to the hapten. As pointed out above, such a result would be contrary to the invention, since an anti-hapten immune response would not affect residual tumor cells remaining after resection or metastasis.

As the Examiner has noted, these patents teach conventional methods for generating an antigen specific antibody response. Such antibodies are useful as diagnostic reagents. The immunized subjects do not develop protective immunity to the immunogen; that is not the intention or the outcome. Thus, one might conclude that by following the teachings of these patents, one would be unlikely to generate a protective immune response.

Furthermore, these references do not teach or suggest at least six administrations or immunizations of haptenized tumor cells (or any pathogenic antigen) to humans at spaced intervals for the treatment of cancer. No objective teaching thus exists in these patents that would suggest to or motivate one of skill in the art to administer antibodies to humans at least six times at spaced intervals in order to treat cancer.

The Examiner has made a number of legal errors to arrive at a conclusion of obviousness based on the combined teachings of these references, primarily by failing to properly articulate the Graham factors. For example, Examiner did not properly consider the scope and content of the prior art, and the differences between the prior art and the claimed invention. *Ruiz*, 57 USPQ2d at 1167. The Examiner further failed to establish the level of ordinary skill in the art, *Id.* at 1168, which Appellant has established through the Braun Declaration as well as through the references cited by the Examiner.

With respect to considering the scope and content of the prior art and the differences between the prior art and the claimed invention, the Examiner failed to articulate "... a reason, suggestion, or motivation in the prior art or elsewhere that would have led one of ordinary skill in the art to combine the references." *Id.* at 1167, *citing In re Rouffet*, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) and *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). The Federal Circuit provides explicit

guidance in *Ruiz* on the factual findings to make in determining a reason, suggestion, or motivation to combine:

> The reason, suggestion, or motivation to combine may be found explicitly or implicitly: 1) in the prior art references themselves; 2) in the knowledge of those of ordinary skill in the art that certain references, or disclosures in those references, are of special interest or importance in the field; or 3) from the nature of the problem to be solved, "leading inventors to look at references relating to possible solutions to that problem."

Id. (citations omitted). The Examiner merely alludes to a "conventional immunization scheduled" (Final Office Action [Exhibit 2], page 4; Paper 36 [Exhibit 4], page 11) without providing any basis for linking a conventional immunization schedule for eliciting diagnostic antibodies to an immunotherapy regimen.

The error here arises from the Examiner falling "into the hindsight trap." *In re Kotzab*, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000). As the Court stated in *Kotzab*, "... to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant." *Id.* at 1316, *citing In re Dance*, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998); *In re Gordon*, 211 USPQ 1125, 1127 (Fed. Cir. 1984). The Antibody Patents teach methods to elicit antibodies to the immunizing agent, e.g., a hapten-like compound such as an advance glycosylation endproduct. Geczy shows that haptenization results in hapten-specific immunity. Neither Murphy nor Berd 1989 suggest at least six administrations of the immunotherapeutic vaccine, much less the advantages of doing so disclosed in

the Examples of the instant application. Thus, the Examiner has "... found prior art statements that in the abstract appeared to suggest the claimed limitation...", *Id.* at 1318, but which, in fact, lack any motivation to modify the teachings of Murphy or Berd 1989 to include that limitation.

With respect to the level of skill in the art, which the Examiner relies on in making this rejection (Final Office Action [Exhibit 2], page 4), Appellant respectfully submits that, in view of the Braun Declaration and the explicit teaching of the references, the level of skill in the art does not supply the missing teaching here. *See A-Site Corp. v. VSI*, 50 USPQ2d 1161, 1171 (Fed. Cir. 1999). "[T]he level of skill in the art is a prism or lens through with a judge or jury views the prior art and the claimed invention. This reference point prevents these deciders from using their own insight or, worse yet, hindsight, to gauge obviousness." *Id.* The Examiner has not established that the level of skill in the art is such that it would lead the skilled artisan to modify the teachings of Murphy or Berd 1989 as set forth in the claim. To rely on "conventional immunization schedules" is therefore error.

The Examiner cited two cases to support her analysis of obviousness. In particular, the Examiner points out that "[t]he test for obviousness...is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 208 USPQ 871, 881 (CCPA 1981) (Citations omitted). Appellant agrees, but points out that the Examiner must consider the references for all that they teach; it is impermissible to consider a reference in less than its entirety,

or to disregard disclosures that diverge and teach away. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 220 USPQ 303 (Fed. Cir. 1993), *cert. denied* 469 U.S. 851 (1984). Such teaching away, which is the effect of the Antibody Patents and Geczy reference, defeats obviousness. *See Winner Int'l Royalty Corp. v. Wang*, 53 USPQ2d 1580, 1587 (Fed. Cir. 2000). Moreover, the prior art, and not the disclosure in the application, must both suggest the invention and provide a reasonable expectation of success in achieving it. *In re Vaeck*, 20 USPQ 2d 1438 (Fed. Cir. 1991).

Correctly applying the foregoing legal principles, the references neither (1) suggest the invention, nor (2) provide a reasonable expectation of success. Berd 1989 and by extension Murphy 1990 are inadequate to suggest modifying the immunization strategy to require at least six administrations of an immunotherapeutic vaccine. Taken together, as the Examiner points out that the references must be considered, the references do not render the claimed invention obvious. The Examiner's failure to properly consider the *Graham* factors, and the admitted use of hindsight to establish obviousness, represent error and should be reversed.

b. The rejection of claims 47, 65-72 and 74-77 over Berd 1989, the Antibody Patents, and Geczy

The Examiner maintained this rejection for the same reasons described in the above rejection. For the reasons set forth above, the combination of Berd 1989,

the Antibody Patents, and Geczy, fails to render the instant invention obvious. Indeed, this rejection is clearly ineffective since Berd 1989 provides even less information about methods of treatment and therapeutic outcomes than Murphy, which the Braun Declaration makes abundantly clear. In short, one of ordinary skill in the art would not have had any motivation to modify the teachings of Berd 1989 to require immunization with the haptenized tumor cell vaccine at least six times. The Examiner has erroneously failed to establish the *Graham* factors sufficient to render the invention obvious, and instead has substituted hindsight to sustain this rejection, both of which constitute error. *See Ruiz*, 57 USPQ2d at 1167-68. Thus, this rejection is in error and should be reversed.

c. The rejection of claims 43, 44, 47, 49-62, 64-72, and 74-77 over Berd 1989, the Antibody Patents, and Geczy in view of Wiseman

Claim 43 is directed to a composition comprising human tumor cells (other than melanoma cells) conjugated with a hapten. The haptenized tumor cells are obtained from the patient receiving treatment (i.e., they are "autologous"), and are rendered incapable of growing in the body of a human upon injection therein.

Claim 44 is directed to a method for treating a malignant tumor (other than melanoma) in a human patient by co-administering a composition comprising haptenized autologous human tumor cells of the same tumor type as the tumor in the

patient, along with an adjuvant. The composition elicits at least one of the following upon administration to the patient with the adjuvant: an inflammatory immune response against the tumor of the patient; a delayed-type hypersensitivity response against the tumor of the patient; and activated T lymphocytes that infiltrate the tumor of the patient.

Claim 47 has been discussed above, as have the references except for Wiseman. The Examiner contends that "Wiseman clearly showed that autologous irradiated melanoma, lung, colon, and kidney cancer were successfully used for successful immunological treatment of those cancers and it would have been expected that these cell types, already known in the art to be useful as immunogenic cancer treatments would be successfully substituted for the melanoma cells of Berd [1989] in order to treat the other cancer types." (Final Office Action [Exhibit 2], paragraph bridging pages 5 and 6).

The Braun Declaration addresses the teachings and deficiencies of Berd 1989, and discussed above. The reference lacks teachings with respect to any clinically significant tumor regression being observed, as well as the numbers and route of administration. (Braun Declaration [Exhibit 16], ¶¶9 and 11). Thus, one of ordinary skill in the art would have presumed that Berd 1989's haptenized tumor cells and BCG had been injected intratumorally, and that the BCG was thereby responsible for the observed, clinically non-significant, tumor responses (Braun Declaration [Exhibit 16],¶11). Accordingly, Berd 1989 suffers from a lack of expectation of success for

the haptenized-tumor-cell approach in melanoma, and even more so in the case of non-melanoma tumors.

As discussed in the previous amendment dated September 22, 2000 (p. 17, 1st full paragraph), Wiseman teaches an alternative form of immunotherapy that depends on the route of administration: intralymphatic immunization. This alternative, which Wiseman indeed reports favorably, in no way suggests a deficiency or problem that would lead one of ordinary skill in the art to seek an alternative immunization strategy.

On the contrary, Wiseman diverts the skilled artisan away from the claimed invention, thus precluding combining this reference in making the rejection. One of ordinary skill in the art would, when provided with the Wiseman reference on one hand and the combination of Berd 1989, The Antibody Patents, and Geczy on the other, the latter themselves leading away from any combination with the haptenized tumor cell compositions and methods because they suggest an anti-hapten rather than anti-tumor cell response, be inclined to pursue the Wiseman approach: intralymphatic immunization with unmodified tumor cells, since this approach was successful and avoided the problems with the haptenization approach in Berd 1989 and suggested by the Antibody Patents and Geczy. Such teaching away, which is the effect of the Antibody Patents and Geczy reference, defeats obviousness. *See Winner Int'l Royalty*, 53 USPQ2d at 1587.

Nothing in Berd 1989 suggests that haptenization of tumor cells provides an effective therapeutic response (as established by the Braun Declaration), much less a more effective response than other immunization protocols. However, the data clearly support the unexpected superiority of the haptenized tumor cells and methods of immunotherapy using them.

> The DFS [disease-free survival] and TS [total survival] of [patients treated with haptenized tumor cells] were compared with those of 22 melanoma patients with resected nodal metastasises treated previously with unconjugated vaccine, see Example 4. Of 36 patients with stage 3 melanoma (palpable mass in one lymph node region), 22 are disease-free with a median follow-up of 33 months. Kaplan-Meir analysis projects a 3 year DFS and TS of 59% and 71%, respectively. In contrast, the DFS and TS of stage 3 patients treated with unconjugated vaccine was 22% and 27% respectively ($p = 0.01$, log-rank test). Of 11 stage 4 patients (palpable mass in two lymph node regions), 5 are NED (no evidence of disease) with a median follow-up of 41 months.

(Specification, page 41, line 24 to page 42, line 8). These data demonstrate the superiority of the claimed invention, particularly the claimed methods of treatment, relative to Wiseman's approach. However, these advantages can only be gleaned from the disclosure of the specification, and are not available from the combined teachings of the references. Advantages flowing directly from the invention are one consideration that may be relevant to a determination of obviousness. *Mosinee Paper Corp. v. James River Corp. of Virginia*, 22 U.S.P.Q.2d 1657, 1660, *aff'd. mem.* 980 F.2d 743 (Fed. Cir. 1992) (citing *Pre-Emption Devices, Inc. v. Minnesota Mining & Mfg. Co.*, 221 USPQ 841 (Fed. Cir. 1984)). "After all, those advantages are the foundation of that 'commercial success' which may be evidence of nonobviousness.

Pre-Emption, supra, at 844 (*citing Graham*, 383 U.S. at 17). Thus, the showing of significant advantages of the presently claimed compositions and methods, particularly as related in Example 6 (quoted above), demonstrates non-obviousness of the invention.

Even if Berd 1989 taught an effective immunotherapy of melanoma using haptenized, autologous melanoma cells, such a teaching would not form a sufficient basis for combination with Wiseman to achieve the claimed invention. As applicants have previously pointed out, it is not expected that "vaccines using other types of tumor cells, shown to effectively treat cancer, would behave in a mechanistically similar manner to the melanoma vaccine described in Berd et al." (See Paper No. 41 [Exhibit 3], page 5, lines 12-14). In the PTO-1449 form filed by Applicant on December 1, 1998, Applicant brought the Examiner's attention to Hanna et al. (U.S. Patent No. 5,484,596, hereinafter "Hanna"). Hanna teaches a method for the treatment of human colon cancer that involves the use of a vaccine which is made from irradiated human tumor cells. The Examiner is requested to note that the Hanna et al. vaccine strategy appears to be effective only for treating colon cancer. A publication reporting on a clinical trial of the "Hanna et al." vaccine concedes that the vaccine was not effective for rectal cancer (Hoover et al., J. Clin. Oncology 11: 390-399, 1993; copy attached to the Amendment filed September 22, 2000 as Exhibit 1 [Exhibit 17]). Hoover et al. states that ". . . no benefits were seen in patients with rectal cancer who received [active specific immunotherapy with an autologous

tumor cell-BCG vaccine]" (see Abstract; see also page 399, first column). Hence, although the Hanna vaccine was reportedly successful in treating colon cancer, it failed to provide any benefits to patients with rectal cancer, a tumor type closely related to colon cancer. Accordingly, even had Berd '89 successfully treated melanoma patients with his haptenized tumor cell vaccine, and not only provided preliminary and essentially anecdotal results relating to DTH-responses, it could not have been reasonably expected that a similar vaccine would be equally effective in the treatment of related tumors, much less tumors of completely unrelated origin.

It is clear that upon careful examination, the references cannot be combined as the Examiner has suggested. Thus, here to the Examiner's citations appear on the surface to suggest the claimed invention, but, upon further review, can only be combined as the Examiner proposes with knowledge of the Applicant's invention. *In re Kotzab*, 55 USPQ2d at 1318. Such an analysis is, of course, improper. For the foregoing reasons, this obviousness rejection is in error and should be reversed.

d. The rejection of claims 43, 44, 47, 49-62, 64-72, and 74-77 over Berd 1989, the Antibody Patents, Geczy, and Berd 1983

Claims 43, 44, and 47 have been discussed above. Berd, the Antibody Patents, and Geczy are discussed above. In addition, the teachings of Berd 1989, the

Antibody Patents, and Geczy have been discussed above. The Examiner states that Berd '83 teaches treatment of breast cancer patients with autologous vaccine, and that the substitution of the breast cancer cells of Berd 1983 for the melanoma cells of Berd 1989 was prima facie obvious.

The Examiner alleges that Appellant has previously argued the Berd 1983 reference individually without clearly addressing the combined teachings. Appellant respectfully disagrees. Appellant chose to, instead of repeating arguments already made in the amendment, discuss the entirety of the teachings of Berd 1983 before adding this reference to the combination of Berd 1989, the Antibody Patents, and Geczy (see amendment dated September 22, 2000, page 18, section 3.g). In doing so, it is clear that Berd 1983 adds nothing to the combination of Berd 1989, The Antibody Patents, and Geczy, which combination is (1) improper and (2) fails to provide any reasonable expectation of success as discussed above.

Berd 1983 teaches the intradermal administration of autologous tumor cells to six cancer patients, five suffering from melanoma and one from breast cancer, and reports DTH responses against tumor cells in three out of the five evaluated patients. Note that Berd 1983 is silent with respect to whether the single breast cancer patient was among the 3 patients (50%) showing a DTH response. Even assuming that the breast cancer patient was among the three, the addition of Berd 1983 to the combination of reference would not provide a reasonable expectation that

a haptenized tumor cell vaccine, whether based on melanoma or breast cancer cells, would elicit a clinically significant anti-tumor response.

The Braun Declaration addresses the teachings and deficiencies of Berd 1989, as discussed above. The reference lacks teachings with respect to any clinically significant tumor regression being observed, as well as the numbers and route of administration. (Braun Declaration [Exhibit 16], ¶¶9 and 11). Thus, one of ordinary skill in the art would have presumed that Berd 1989's haptenized tumor cells and BCG had been injected intratumorally, and that the BCG was thereby responsible for the observed, clinically non-significant, tumor responses (Braun Declaration [Exhibit 16],¶11). Accordingly, Berd 1989 suffers from a lack of expectation of success for the haptenized-tumor-cell approach in melanoma, and even more so in the case of non-melanoma tumors.

As noted above, even if Berd 1989 taught an effective immunotherapy of melanoma using haptenized, autologous melanoma cells, such a teaching would not form a sufficient basis for combination with Berd 1983 to achieve the claimed invention. As applicants have previously pointed out, it is not expected that "vaccines using other types of tumor cells, shown to effectively treat cancer, would behave in a mechanistically similar manner to the melanoma vaccine described in Berd et al." (See Paper No. 41 [Exhibit 3], page 5, lines 12-14). In the PTO-1449 form filed by Applicant on December 1, 1998, Applicant brought the Examiner's attention to Hanna et al. (U.S. Patent No. 5,484,596, hereinafter "Hanna"). Hanna teaches a method for

the treatment of human colon cancer that involves the use of a vaccine which is made from irradiated human tumor cells. The Examiner is requested to note that the Hanna et al. vaccine strategy appears to be effective only for treating colon cancer. A publication reporting on a clinical trial of the "Hanna et al." vaccine concedes that the vaccine was not effective for rectal cancer (Hoover [Exhibit 17]). Hoover et al. states that ". . . no benefits were seen in patients with rectal cancer who received [active specific immunotherapy with an autologous tumor cell-BCG vaccine]" (see Abstract; see also page 399, first column). Hence, although the Hanna vaccine was reportedly successful in treating colon cancer, it failed to provide any benefits to patients with rectal cancer, a tumor type closely related to colon cancer. Accordingly, even had Berd '89 successfully treated melanoma patients with his haptenized tumor cell vaccine, and not only provided preliminary and essentially anecdotal results relating to DTH-responses, it could not have been reasonably expected that a similar vaccine would be equally effective in the treatment of related tumors, much less tumors of completely unrelated origin.

It is clear that upon careful examination, the references cannot be combined as the Examiner has suggested. Thus, here to the Examiner's citations appear on the surface to suggest the claimed invention, but, upon further review, can only be combined as the Examiner proposes with knowledge of the Applicant's invention. *In re Kotzab*, 55 USPQ2d at 1318. Such an analysis is, of course,

improper. For the foregoing reasons, this obviousness rejection is in error and should be reversed.

e. The rejection of claims 43, 44, 47, 49-62, 64-72, and 74-77 over Berd, the Antibody Patents, Geczy, and Sanda and Moody

Claims 43, 44, and 47 have been discussed above. Berd, the Antibody Patents, and Geczy are discussed above. In addition, the teachings of Berd 1989, the Antibody Patents, and Geczy have been discussed above. The Examiner has stated that in particular Berd supplies the motivation to "decorate the tumor cells with hapten." Incorporating the reasoning set forth in the prior two Office Actions, the Examiner states that Moody teaches that lymphokine-transfected prostate cells generate an anti-tumor effect *in vivo*, and that Sanda addresses the feasibility of gene therapy for human prostate cancer. These references appear to be relevant to the Examiner because they suggest methods of anti-prostate cancer therapy.

Sanda teaches a method for transducing human prostate cancer cells with a particular retroviral vector. The method was reportedly successful for transfecting the cells, and Sanda suggest that this approach may be feasible in gene therapy of prostate cancer. Although Sanda fails to provide any description on just how his approach would be used in gene therapy and why, the general approach in gene therapy is to administer a gene, locally or systemically, to a patient in an attempt to

transfect cells *in vivo* for some therapeutic purpose. This approach is wholly unrelated to any immunotherapeutic method for cancer treatment, and therefore cannot add anything to the combination of references cited in this rejection. It solves a different problem (tumor cell ablation through a therapeutic gene) than the claimed invention (tumor cell immunotherapy using a haptenized tumor cell as a vaccine). Thus, there is no logical connection between Sanda and the other references cited in this rejection. *See Ruiz*, 57 USPQ2d at 1168 (evidence that the references solve different problems can preclude a determination of obviousness).

Moody teaches an immunotherapy method based on lymphokine expression in which rat prostate tumor cells were transfected with cDNA encoding IL-2 and IL-4, the transfected tumor cells were administered to rats, and tumor immunity observed in the treated rats as compared to controls. This references adopts an altogether different approach than haptenization of tumor cells to elicit tumor cell immunity.[5] There is no suggestion from Moody to modify the approach it teaches by haptenizing the prostate tumor cells.

In short, for the reasons discussed above, the combination of Berd 1989, the Antibody Patents, and Geczy fail to suggest, much less teach, compositions of haptenized tumor cells (that are not melanoma cells), methods of cancer

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[5] As disclosed in the specification of the instant application, using immunostimulatory molecules in <u>combination</u> with the claimed compositions and methods may be desirable in some instances. (Specification, page 17, lines 17-20). Moody provides one avenue for such a combination. This in no way suggests the claimed invention.

immunotherapy using haptenized tumor cells (especially that are not melanoma cells as recited in claim 44), or methods of cancer immunotherapy involving a regimen of administering haptenized tumor cells at least six times. Sanda and Moody have nothing to do with immunotherapy; they are in this respect less relevant than Wiseman. Accordingly, for the reasons advanced above, this rejection is in error and must be reversed.

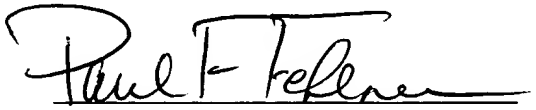
It is clear that upon careful examination, the references cannot be combined as the Examiner has suggested. Thus, here to the Examiner's citations appear on the surface to suggest the claimed invention, but, upon further review, can only be combined as the Examiner proposes with knowledge of the Applicant's invention. *In re Kotzab*, 55 USPQ2d at 1318. Such an analysis is, of course, improper. For the foregoing reasons, this obviousness rejection is in error and should be reversed.

9. Conclusion

For the forgoing reasons, Appellant submits that the Final Rejection is in error and should be reversed on all grounds. The Examiner has committed error by failing across the board to properly articulate the *Graham* factors. For example, Examiner did not properly consider the scope and content of the prior art, and the differences between the prior art and the claimed invention. *Ruiz*, 57 USPQ2d at

1167. The Examiner further failed to establish the level of ordinary skill in the art, *Id.* at 1168, which Appellant has established through the Braun Declaration as well as through the references. With respect to considering the scope and content of the prior art and the differences between the prior art and the claimed invention, the Examiner failed to articulate "... a reason, suggestion, or motivation in the prior art or elsewhere that would have led one of ordinary skill in the art to combine the references." *Id.* at 1167 (citations omitted). Instead, the Examiner has improperly relied on the level of skill in the art to fill in the holes in the prior art, *See A-Site Corp.* 50 USPQ2d at 1171, and has consistently fallen into the "hindsight trap". *In re Kotzab*, 55 USPQ2d at 1318.

Respectfully submitted,



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APPENDIX

Pending Claims on Appeal

43. (Amended) A composition comprising human tumor cells that:

(i) are conjugated to a hapten;

(ii) are of the same tumor type as a malignant tumor of a patient for treatment of whom the composition is intended;

(iii) are autologous to said patient; and

(iv) have been rendered incapable of growing in the body of a human upon injection therein;

said composition eliciting, when administered together with an adjuvant, an inflammatory immune response against the tumor of said patient, wherein said tumor is not melanoma.

44. A method for treating a malignant tumor in a human patient comprising co-administering to the patient

(a) a composition comprising a therapeutically effective amount of human tumor cells that:

(i) are conjugated to a hapten;

(ii) are of the same tumor type as a malignant tumor of a patient for treatment of whom the composition is intended;

(iii) are autologous to said patient; and

(iv) have been rendered incapable of growing in the body of a human upon injection therein; and

(b) an adjuvant;

wherein said composition elicits at least one of the following upon administration to said patient with the adjuvant: an inflammatory immune response against the tumor of said patient; a delayed-type hypersensitivity response against the

tumor of said patient, and activated T lymphocytes that infiltrate the tumor of said patient, wherein said malignant tumor is not melanoma.

47. (Amended) A method of treating a malignant tumor in a human patient comprising co-administering to the patient

(a) a composition comprising a therapeutically effective amount of human tumor cells that:

(i) are conjugated to a hapten;

(ii) are of the same tumor type as a malignant tumor of a patient for treatment of whom the composition is intended;

(iii) are autologous to said patient; and

(iv) have been rendered incapable of growing in the body of a human upon injection therein; and

(b) an adjuvant;

wherein said composition elicits at least one of the following upon administration to said patient with the adjuvant: an inflammatory immune response against the tumor of said patient; a delayed-type hypersensitivity response against the tumor of said patient and activated T lymphocytes that infiltrate the tumor of said patient; and

repeating said administration at least six times at spaced apart intervals.

49. The composition of claim 43 wherein said tumor cells are selected from lung, colon, breast, kidney, and prostate tumor cells.

50. The composition of claim 43 wherein said hapten is selected from the group consisting of dinitrophenyl, trinitrophenyl, and N-iodoacetyl-N'-(5 sylfonic 1-naphtyl) ethylene diamine.

51. The composition of claim 43 wherein said hapten is dinitrophenyl.

52. The composition of claim 43 further comprising an adjuvant.

53. The composition of claim 52 wherein said adjuvant is Bacillus Calmette-Guerin.

54. The composition of claim 43 further comprising a carrier.

55. The composition of claim 54 wherein said carrier is selected from the group consisting of saline solution and culture medium.

56. The method of claim 44 wherein said tumor cells are selected from lung, colon, breast, kidney, and prostate tumor cells.

57. The method of claim 44, wherein said malignant tumor is from a cancer selected from the group consisting of lung cancer, colon cancer, breast cancer, kidney cancer, and prostate cancer.

58. The method of claim 44 wherein said hapten is selected from the group consisting of dinitrophenyl, trinitrophenyl, and N-iodoacetyl-N'-(5-sulfonic 1-naphtyl) ethylene diamine.

59. The method of claim 44 wherein said hapten is dinitrophenyl.

60. The method of claim 44 further comprising administering a therapeutically effective amount of cyclophosphamide prior to administration of said composition.

61. The method of claim 60 wherein said therapeutically effective amount of cyclophosphamide comprises administering a dose of about 300 mg/M2 of cyclophosphamide prior to administration of said composition.

62. The method of claim 60 further comprising sensitizing the patient with a therapeutically effective amount of 1-fluoro-2,4-dinitrobenzene prior to administering cyclophosphamide.

64. The method of claim 44 wherein said adjuvant is Bacillus Calmette-Guerin.

65. The method of claim 47 wherein said tumor cells are selected from melanoma, lung, colon, breast, kidney, and prostate tumor cells.

66. The method of claim 47, wherein said malignant tumor is from a cancer selected from the group consisting of melanoma cancer, lung cancer, colon cancer, breast cancer, kidney cancer, and prostate cancer.

67. The method of claim 47 wherein said hapten is selected from the group consisting of dinitrophenyl, trinitrophenyl, and N-iodoacetyl-N'-(5-sulfonic 1-naphtyl) ethylene diamine.

68. The method of claim 47 wherein said hapten is dinitrophenyl.

69. The method of claim 47 further comprising administering a therapeutically effective amount of cyclophosphamide prior to administration of said composition.

70. The method of claim 47, further comprising administering a therapeutically effective amount of cyclophosphamide prior to the first administration of said composition.

71. The method of claim 69 wherein said therapeutically effective amount of cyclophosphamide comprises administering a dose of about 300 mg/M2 of cyclophosphamide prior to administration of said composition.

72. The method of claim 47 further comprising sensitizing the patient with a therapeutically effective amount of 1-fluoro-2,4-dinitrobenzene prior to administering cyclophosphamide.

74. The method of claim 47 wherein said adjuvant is Bacillus Calmette-Guerin.

75. The method of claim 47 wherein said administration prolongs survival of said patient.

76. The method of claim 44, wherein said administration elicits T lymphocytes that infiltrate the tumor of said human, said lymphocytes being predominantly CD8 + CD4 .

77. The method of claim 47, wherein said administration elicits T lymphocytes that infiltrate the tumor of said human, said lymphocytes being predominantly CD8 + CD4 .